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Nivolumab for relapsed/refractory classical Hodgkin lymphoma after brentuximab vedotin failure – Polish Lymphoma Research Group real-life experience

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Abstract

Aim: Polish centers analyzed retrospectively the real-life experience with nivolumab in relapsed/refractory (R/R) classical Hodgkin lymphoma (cHL) patients, after brentuximab vedotin (BV) failure. Background: Despite the effective frontline treatment, for cHL patients relapsing after autologous stem cell transplantation, the only effective strategy remains the novel agents. Nivolumab, a checkpoint inhibitor, demonstrates the clinical benefit with an acceptable safety profile. Materials and methods: Retrospective analysis included 16 adult patients with R/R cHL after BV failure. All patients received single-agent nivolumab 3 mg/kg every 2 weeks until disease progression or unacceptable toxicity. Results: After six cycles of nivolumab the overall response rate was 81% (complete remission rate of 56%, partial remission rate of 25%). The median PFS was not reached after a median follow-up of 19 months. Adverse events (AEs) of any grade occurred in 12 patients (75%), including grade 3 AEs observed in 5 patients (31%). There were no AEs of grade 4 or 5. After a median of 25 nivolumab doses, 62% of responding patients proceeded to allogeneic stem cell transplantation. Conclusion: Nivolumab monotherapy demonstrated a high efficacy and safety in R/R cHL patients after BV failure. More patients and longer follow-up may further establish the potential benefit.

Keywords:
checkpoint inhibitor, Hodgkin Lymphoma, nivolumab, refractory, relapsed

Introduction

Despite the effective frontline treatment of classical Hodgkin lymphoma (cHL), about 10% of early-stage and 30% of advanced stage patients experience disease relapse or have refractory disease [1]. Only half of relapsed/refractory (R/R) patients can be cured with salvage chemotherapy followed by high-dose chemotherapy (HDT) and autologous stem cell transplantation (ASCT) [2]. For patients relapsing after second-line treatment, the possible effective therapy option can be salvage treatment with novel agents that have emerged in recent years. Histopathologically cHL is characterized by minority of malignant cells represented by clonal malignant Hodgkin and Reed-Sternberg (HRS) cells and the domination of inflammatory and immune cells [3, 4]. The HRS cells present the expression of CD30 antigen and produce molecules inhibiting T-cell-mediated immune response [5]. HRS cells achieve immune evasion by multiple mechanisms including enhanced expression of programmed cell death-1 ligands (PD-L1 and PD-L2) that bind programmed cell death protein 1 (PD-1) on the surface of antigen-experienced T cells to suppress T-cell activation [6]. Considering the molecular mechanism of action in cHL, in multiply relapsed settings the major targets are CD30 expressed by HRS cells and PD-1, PD-L1 and PD-L2 which are overexpressed in HRS cells due to chromosome 9p24.1 amplification [5]. The breakthrough in the therapy of R/R cHL was the development of brentuximab vedotin (BV), an antibody-drug conjugate (ADC) targeting the CD30 antigen and demonstrating activity as salvage regimen, after ASCT and even after allogeneic stem cell transplantation (allo-SCT) failure [7-10]. Nivolumab is an IgG4 fully human anti-PD-1 monoclonal antibody (mAb) with proven efficacy in a number of solid tumors. Its activity was first demonstrated in R/R cHL in a phase I CheckMate 039 study [11] and further supported by the results of phase II, CheckMate 205 study conducted in BV-naïve and relapsed after BV-ASCT combination [12]. The results of these studies led to the approval of nivolumab in monotherapy by the Food and Drug Administration (FDA) [13] and by the European Medicines Agency (EMA) [14] for R/R cHL patients who failed ASCT and BV or who are transplant-ineligible and have failed BV.

The objective of this retrospective analysis was to evaluate the efficacy and safety of nivolumab in R/R cHL patients after BV failure (real-life experience).

Material and methods

In this retrospective analysis, we collected the data of 16 R/R cHL adult patients treated with single-agent nivolumab as salvage regimen in 5 Polish Lymphoma Research Group (PLRG) centers. Nivolumab was administered after failure of BV treatment. The diagnosis according to the World Health Organization 2008 classification, was based on histopathological assessment of tissue samples excised before the first-line therapy [15]. At baseline staging according to Ann Arbor classification, Eastern Cooperative Oncology Group

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performance status (ECOG PS) and International Prognostic Index (IPI) were assessed.

Patients received nivolumab intravenously over 60 minutes at 3 mg/kg every 2 weeks until disease progression or unacceptable toxicity. Efficacy data including overall response rate (ORR), complete remission (CR) rate, progression-free survival (PFS) and overall survival (OS) as well as the safety data were collected. Computed tomography (CT) scans of neck, chest, abdomen and pelvis were obtained before therapy, 3 months after starting treatment and repeated every 6 months. 18F-fluorocholine deoxyglucose positron emission tomography (PET) combined with computed tomography (PET-CT) was performed before nivolumab treatment and for confirmation of suspected progressive disease (PD). Response evaluation was performed according to 2014 Lugano classification [16]. Eligible patients with objective response to treatment were considered for consolidation with either HDT/ASCT or allo-SCT according to the local policy. For patients who discontinued nivolumab to proceed to transplantation, disease assessment (CR, non-CR) was performed according to local standards and clinical symptoms. The data on the transplantation and graft-versus-host-disease (GVHD) were collected. HDT platinum-based and ifosfamide-containing regimens [17-22] and myeloablative conditioning were administered according to standard criteria [23]. Supportive treatment was administered as required according to the local standards, including adequate fluid intake and allopurinol for tumor lysis syndrome prevention. Safety outcomes were the incidence of adverse events (AEs), classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03 [24]. To characterize the study group and response to therapy we used descriptive statistical methods. Survival analysis was performed by Kaplan-Meier method; both PFS and OS were calculated from the time Nivolumab therapy was initiated to time of progression, death from any cause or the date of the last follow-up. Statistical analyses were performed using the software Statistica, version 10 (StatSoft, Krakow, Poland).

Results

Between September 2016 and November 2018, a total of 16 adult patients with R/R cHL received single-agent nivolumab at 5 Polish sites. Overall, 38% (6/16) of the patients were men, 50% (8/16) had stage IV disease, 44% (7/16) presented extranodal involvement at diagnosis and 81% (13/16) had B symptoms as weight loss, night sweats or fever. The median age at the start of treatment was 30 years (range 18-51), median IPI score was 4 (range 2-6). The following histopathological subtypes were diagnosed: nodular sclerosis (NS), mixed cellularity (MC) and lymphocyte depleted (LD) in 88% (14/16), 12% (1/16) and 12% (1/16) of patients, respectively. The patients did not present any other immune diseases at the start of nivolumab treatment. Patient characteristics and demographics are presented in table I.

As frontline regimen 75% (12/16) of patients were treated with 6 cycles of ABVD (adriamycin, bleomycin, vinblastine and dacarbazine), 25% (4/16) with 2 cycles of dose-escalated BEACOPP (escBEACOPP) (bleomycin, etoposide, adriamycin, cyclophoshamide, vincristine, procarbazine and prednisone) followed by 4 cycles of ABVD.

Table I. Baseline patient and disease characteristics

Patient Demographics	
Male, n (%)	6 (38)
Female, n (%)	10 (62)
Median age, years (range)	30 (18-51)
Median number of prior treatments, n (range)	3 (2-6)
Histologic subtype n (%)	
NS	14 (86)
MC	1 (12)
LD	1 (12)
ECOG PS n (%)	
0-1	12 (75)
≥ 2	4 (25)
Stage, n (%)	
I	0 (0)
II	7 (44)
III	1 (6)
IV	8 (50)
B symptoms, n (%)	13 (81)
Bulky disease, n (%)	11 (69)
Extranodal involvement, n (%)	44 (7)
Median IPI, number (range)	4 (2-6)
Disease status	
Primary refractory, n (%)	6 (37)
Relapsed, n (%)	10 (62)
ASCT before nivolumab, n (%)	44 (7)

ASCT – autologous stem cell transplantation, ECOG PS – Eastern Cooperative Oncology Group Performance Status, IPI – International Prognostic Index, LD – lymphocyte depleted, MC – mixed cellularity, NS – nodular sclerosis

6 patients (37%) had primary refractory disease not responding to standard regimen and BV. All patients failed BV after the median number of cycles equal to 7 (range 2-16), with 56% (9/16) refractory to BV. The median number of prior to BV lines of therapy was 2 (range 2-3). The median age at the start of BV treatment was 28 years (range 18-50). Because the entire group was treated with both BV and nivolumab, the distribution of histopathological subtypes of cHL concerns both groups. Prior to BV 31% (5/16) of patients relapsed after ASCT. Median time between the last dose of brentuximab vedotin and the first dose of nivolumab was 7 months (range 1-47). Prior to nivolumab 44% (7/16) of patients relapsed after ASCT. The median number of prior lines was 3 (range 2-6). Radiotherapy was carried out in 56% (9/16) of patients. The median number of nivolumab cycles was 29 (range 3-34). There were no dose reductions or dosing interruptions. After six cycles of nivolumab ORR was 81% (13/16) with a CR rate of 56% (9/16) and partial remission (PR) rate of 25% (4/16). Three patients (19%) had a stable disease (SD) and progressed after 12 cycles of nivolumab. One of responding patients (8%), having achieved PR experienced progressive disease after 19 cycles of nivolumab. Among patients, who were refractory to BV, nivolumab treatment resulted with ORR in 67% (6/9). The main reason for discontinuation was progressive

disease (25%, 4/16) and allo-SCT (50%, 8/16). The median PFS was not reached after a median follow-up of 19 months, estimated PFS at 20 months was 72% (Fig. 1), with a statistically significant difference compared to BV treatment ($p < 0.05$) (Fig. 2). During observation 3 patients died; one from disease progression, next two patients due to complications after allo-SCT. All deaths were not related to nivolumab therapy. During nivolumab treatment, adverse events of any grade occurred in 12 patients (75%), including grade-3 AEs observed in 5 patients (31%) (Tab. II). The most common drug-related AEs of any grade were fatigue, rash and diarrhea. Infusion-related reactions (IRR) grade 2 were observed in 3 patients (19%) and did not cause treatment interruption. There were no AEs of grade 4 or 5. The details of AEs are summarized in table II.

In total, 8 patients (62% of responding patients) stopped nivolumab treatment and proceeded to allo-SCT after a median of 25 nivolumab doses (6 patients from sibling donors, 2 from matched unrelated donors). Responses at the time of transplantation were only complete remission. Most patients (75%, 6/8) received nonmyeloablative conditioning. Median time from the last dose of nivolumab to allo-SCT was 20 days. Median follow-up after allo-SCT was 6 months. Acute graft versus host disease (aGVHD) was not reported. Cutaneous chronic graft versus host disease (cGVHD) was noted in 2 patients. After allo-SCT 2 patients died; the first one because of thrombotic thrombocytopenic purpura (TTP), the second one due to massive mycosis and fungal pneumonia. We did not observe disease progressions after allo-SCT.

Discussion

Outcomes for patients with cHL have improved significantly over the last decades thanks to the effective frontline chemotherapy such as ABVD or escBEACOPP [25]. However, R/R cases, both in the pretransplant setting and relapsing after ASCT, have a high priority to the use of novel agents, not only short-term effective, but also overcoming disease resistance. In the pivotal phase II study, BV has shown significant clinical efficacy in R/R cHL patients after ASCT with ORR of a75%, CR of 34% and a median PFS of 9.3 months [7, 26]. Patients who are refractory or relapse after BV therapy are a challenge. PD-1 blocking antibodies now represent a major breakthrough in the treatment of R/R cHL after ASCT and BV. After the encouraging data from extended analysis of three CheckMate 205 cohorts [27], confirming the efficacy and favorable safety profile

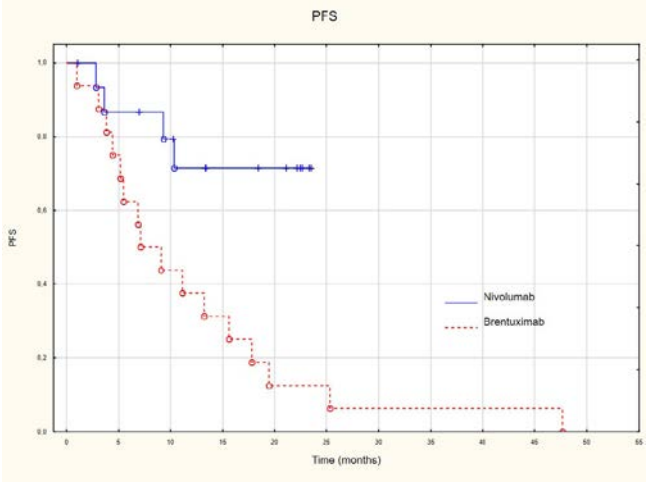

Fig. 1. Progression-free survival in the analyzed group

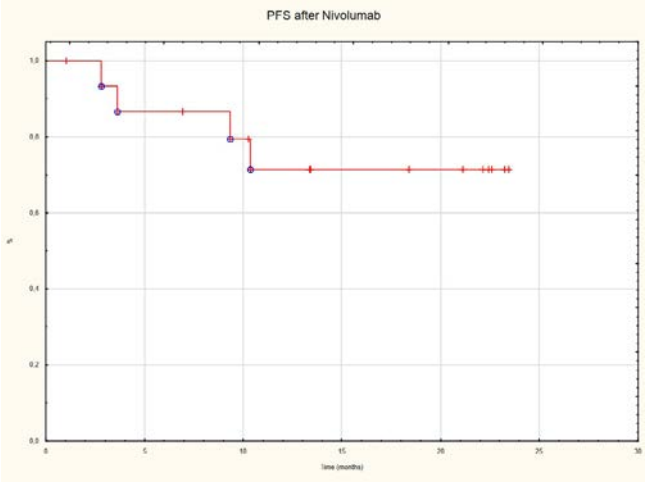

Fig. 2. Comparison of progression-free survival after brentuximab vedotin and nivolumab treatment

Table II. Adverse events, according to CTCAE ver 4.03

Adverse event	All grade n (%)	Grade 1, n (%)	Grade 2, n (%)	Grade 3, n (%)	Grade 4, n (%)
ADVERSE EVENTS					
Fatigue	4 (25)	1 (6)	1 (6)	2 (12)	0
Rash	2 (12)	0	1 (6)	1(6)	0
Diarrhea	2 (12)	0	1 (6)	1 (6)	0
Neutropenia	1 (6)	0	0	1 (6)	0
Pneumonia	1 (6)	0	1 (6)	0	0
Pyrexia	1 (6)	1 (6)	0	0	0
Lipase increased	1 (6)	0	1 (6)	0	0
INFUSION-RELATED REACTIONS					
Infusion-related reactions	3 (19)	0	3 (19)	0	0

of nivolumab in R/R cHL patients, the efficacy of PD-1 blockade in R/R cHL was supported by the phase II study with pembrolizumab [28] .

Our real-life experience with nivolumab in R/R cHL patients who failed after BV therapy, showed a higher response rate (81%) and CR rate (56%) comparing to similar population of patients from cohort C of Checkmate205 study (patients after BV and/or ASCT, with 69% ORR and 12% CR) [27]. CR rates were assessed by CT scans, we did not perform PET assessment to confirm CR, because the immune reactions within tumours that may have contributed to persistence of fluorodeoxyglucose (FDG) uptake and thereby understate the CR rate [12]. We understand that in real-life the confirmation of CR was carried out by investigators, not the independent reviewers, however the results are encouraging, though needing further observation and evaluation. Furthermore, it is worth noting, that the high percentage of responders was obtained in patients refractory to BV (67%). It may be related to the mechanism of PD-1 blockade, completely different from the mechanism of cytostatics and ADC such as BV.

The role of allo-SCT consolidation after anti-PD-1 treatment is still unclear because of the higher risk of GVHD [11, 12]. On the other hand, there are limited therapeutic options available in the case of disease relapse. At this time it is difficult to make any conclusions regarding the use of nivolumab as a bridge to allo-SCT, but certainly transplantation continues to be a therapeutic option for these patients [12, 27]. In a phase 1 study four of five patients died following complications after allo-SCT [12]. In Polish experience the results are much better. Eight patients proceeded to transplantation, two of them (25%) died due to complications related to allo-SCT, but six are still alive (75%), with no chance for survival in the pre-nivolumab era. Nivolumab demonstrated an accaptable safety profile in clinical trials and in real-life. We did not qualify to nivolumab therapy patients with a diagnosis of active autoimmune diseases, receiving systemic full dose corticosteroids or immunosuppressive therapy due to the higher risk of autoimmune toxicities. In the analysis of 52 advanced melanoma patients with preexisting autoimmune disorders, treatment with nivolumab induces 30% autoimmune diseases with the majority of rheumatoid disorders [29]. Interestingly, the use of immunosupressive drugs resulted in lower response rates [29]. The AEs rate in our analysis was favorable; reported events were menegable and acceptable. AEs were mainly grade 1-2, grade 3 AEs occured in 31% of patients and resolved after supporting treatment. Grade 4-5 AEs were not reported.

The study has limitations, due to its retrospective character, limited number of patients and short follow-up period. Further evaluation of optimal length of treatment, possibility to continue treatment beyond progression until clinical benefit is maintained is needed.

In conclusion, the data from this retrospective analysis confirm the high efficacy and safety of nivolumab monotherapy in heavily pretreated R/R cHL patients in routine clinical practice. Nivolumab – a novel drug potentially transforming the treatment landscape in HL, may provide long-term benefits to a group of patients deprived of other effective options. Sustained benefits were seen across different populations including primary refractory patients, relapsed after ASCT or refractory to BV. Presented by us analysis lend further support confirming the hypothesis of durable benefit from PD-1 blockage, even in primary refractory patients. The long-term follow-up is required to provide additional information on the real-life efficacy, safety and outcomes of post-allo-SCT patients after PD-1 blockade.

Abbreviations

ABVD – adriamycin, bleomycin, vinblastine and dacarbazine
ADC – antibody-drug conjugate
AE – adverse event
aGVHD – acute graft versus host disease
Allo-SCT – allogeneic stem cell transplantation ASCT – autologous stem cell transplantation BV – brentuximab vedotin
cHL – classical Hodgkin lymphoma
cGVHD – chronic graft versus host disease
CR – complete remission
CT – computed tomography
CTCAE – Common Terminology Criteria for Adverse Events
ECOG PS – Eastern Cooperative Oncology Group Performance Status
EMA – European Medicines Agency
escBEACOPP – dose-escalated BEACOPP - bleomycin, etoposide, adriamycin, cyclophoshamide, vincristine, procarbazine and prednisone
FDA – Food and Drug Administration
FDG – fluorodeoxyglucose
HDT – high dose chemotherapy HRS - Hodgkin and Reed-Sternberg
IPI – International Prognostic Index IRR – infusion-related reaction
LD – lymphocyte depleted mAb – monoclonal antibody MC – mixed cellularity
NS – nodular sclerosis
ORR – overall response rate
OS – overall survival
PD – progressive disease
PD-1 – programmed cell death protein 1
PD-L1 – programmed death-ligand 1
PD-L2 – programmed death-ligand 2
PET – 18F-fluorocholine deoxyglucose positron emission tomography
PET-CT – 18F-fluorocholine deoxyglucose positron emission tomography combined with computed tomography
PFS – progression-free survival
PLRG – Polish Lymphoma Research Group
PR – partial remission R/R – relapse/refractory SD – stable disease
TTP – thrombotic thrombocytopenic purpura

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Authors' contributions/Wkład autorów

MDD, MS, WJ – performed the study and analyzed the data,
MDD, WJ, MS, JF, JR, AŁD, JM, KD – had a substantial contribution to the conception and design of the work,
MDD, MS – drafted the manuscript,
MDD, WJ, MS – critically revised the manuscript for important intellectual content,

MDD, WJ, MS, JF, JR, AŁD, JM, KD – had a substantial contribution to the acquisition, analysis and interpretation of data for the work.

Conflict of interest/Konflikt interesu

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agreed with the content of the manuscript as written. All authors declare no conflict of interest.

Ethics/Etyka

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

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